(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 356 143 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89308352.7

(22) Date of filing: 17.08.89

(51) Int. Cl.5: A 61 K 31/44
A 61 K 47/00, A 61 K 9/00

(30) Priority: 18.08.88 JP 205100/88

(43) Date of publication of application:
28.02.90 Bulletin 90/09

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

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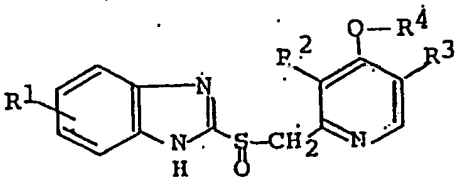
(54) Injectable solutions.

(57) An injectable solution of a compound useful as an anti-ulcer agent of the formula;



wherein R^1 represents hydrogen, methoxy or trifluoromethyl group; R2 and R^3, being the same as or different from each other, represent hydrogen or methyl group; and R^4 represents a fluorinated C_2 to C_5 lower alkyl group, is provided by dissolving the compound in at least one of ethanol, propylene glycol and polyethylene glycol; or by dissolving the freeze-dried material of an alkaline solution aqueous solution of the compound in a mixture of an acidic substance and at least one of the above solvents.

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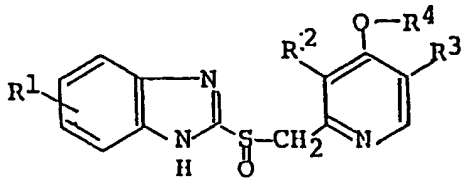
Description

Injectable solutions

This invention relates to injectable solutions containing pyridine derivatives (hereinafter referred to, in some instances, as "Compound (I)") of the below-described formula which are useful as an anti-ulcer agent:



[wherein R^1 represents hydrogen, methoxy or trifluoromethyl; R^2 and R^3, each being the same as, or different from, the other, represent hydrogen or methyl; and R^4 represents fluorinated C_2 to C_6 lower alkyl)

There have been known injectable solutions (refer to The European Unexamined Patent Publication No. 124495), which are obtained by dissolving omeprasol sodium salt having anti-ulcer activity in sterilized water, followed by filtration and lyophilization to give a lyophilized material, which is then dissolved in a sterile-filtered mixed solution of polyethylene glycol 400 for injection, sodium dihydrogenphosphate and sterilized water.

In developing injectable solutions of Compound (I), there are encountered some problems being attributable to its characteristic properties.

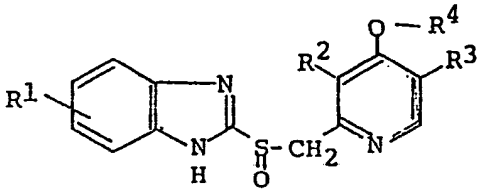
Out of Compound (I), for example, 2-(3-methyl-4-trifluoroethoxy-2-pyridyl)methylsulfinylbenzimidazole (hereinafter referred to briefly as "Compound (I-1)) shows a certain degree of solubility in water but only in the strongly alkaline region of pH 11 or more, with an extremely low solubility in the pH range below pH 11 (33 mg/ml at pH 13, 1 mg/ml at pH 11 and 0.06 to 0.0 1 mg/ml at pH 9 to 3). Referring to the stability in an aqueous solution, Compound (I-1) is satisfactorily stable in an alkaline solution, but becomes less stable according as a pH of the aqueous solution is decreased to the neutral to acid range, while the resulting solution turns in appearance dark purple in a short period of time.

Thus, Compound (I), because of its characteristic properties as described above, have been difficult to process into the dosage form of injectable solution at the physiologically allowable pH range using water alone as a solvent and without employing the sophisticated processing technique, because injectable solutions favorably exhibit a pH value not being far from neutrality in terms of hemolysis, pain or local irritation.

In view of these circumstances described above, the present inventors, after extensive investigation, found that Compound (I) is very soluble in solvents, such as ethanol, propylene glycol and polyethylene glycol, with its stability in said solvents being excellent, and that the powder produced by lyophilizing an alkaline solution of Compound (I) does not tend to discolor with a length of time elapsed and is extremely soluble in the above solvents, and the findings, coupled with further research, have culminated into the present invention.

Thus, the present invention is directed to;

(1) Injectable solutions containing (a) a compound of the formula (I):



(I)

[wherein R^1 represents hydrogen, methoxy or trifluoromethyl; R^2 and R^3, each being the same as or different from the other, represent hydrogen or methyl; and R^4 represents fluorinated C_2 to C_6 lower alkyl] and (b) at least either one of ethanol, propylene glycol and polyethylene glycol; and

(2) Injectable solutions consisting of a lyophilized material of an alkaline solution of Compound (I) being dissolved in a mixed solution composed of (a) an acid substance and (b) at least one of ethanol, propylene glycol and polyethylene glycol.

In the above-described formula, examples of the fluorinated C_2 to C_5 lower alkyl represented by R^4 include 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl, 1,1,1-trifluoromethyl-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl, 2,2,3,3,4,4,5,5-octafluoropentyl and the like. In the above formula, preferably, R^1 and R^3 are hydrogen, and R^2 is methyl, with R^4 being 2,2,2-trifluoroethyl.

It is to be noted that the above-mentioned Compound (I) is a known compound as decribed in The European Unexamined Patent Publication No. 174726.

As the said polyethylene glycol, there can be used polyethylene glycols having varied average molecular

weights, and favorably usable are those having preferably an average molecular weight of 50 to 2000, more preferably an average molecular weight of 100 to 600.

In the present invention, in cases where ethanol, propylene glycol and polyethylene glycol are used as an admixture of more than two kinds, their mutual mixing ratio may be any proportions.

When water is contained in the solvent, an increased proportion of water in the total volume of solvent results in a lowered solubility of Compound (I); particularly in the case of Compound (I) being dissolved in the solvent composed of ethanol and water, the dissolved Compound (I) in some instances separates out with a length of time elapsed, and consequently, the proportion of water in the total volume of solvent is desirably not more than 80 % (V/V).

The injectable solutions according to the present invention can be obtained by dissolving Compound (I) in the form of amorphous powder or crystalline powder into the above-mentioned solvent, but it is preferable to dissolve a lyophilized material of an alkaline aqueous solution of Compound (I) into a mixed solution composed of an acidic substance and the above-mentioned solvent.

As the alkaline aqueous solution of Compound (I), there may be mentioned, for example, an aqueous solution produced by dissolving into water Compound (I) in conjunction with a strongly basic substance such as sodium hydroxide, potassium hydroxide, sodium carbonate and arginine, and adjusting the resulting solution to a pH of not less than 11, preferably not less than 12.

Among the strongly basic substances, sodium hydroxide is particularly preferred.

The concentration of Compound (I) in the said alkaline aqueous solution may be of any concentration only if it permits lyophilization, and is preferably 2 to 30 mg/ml, more preferably 5 to 30 mg/ml.

In order to provide the resulting lyophylized material with improved solid-forming property, it is preferred to add to the alkaline aqueous solution of sucrose, and lactose, neutral amino acids, such as glycine, alanine, proline, valine and methionine, inorganic salts, such as sodium succinate, and the like. These additives can be employed usually in an amount of 0.2 to 5 mg, preferably 0.5 to 3 mg, per mg of Compound (I).

Out of these solid-forming agents, mannitol and glycine are preferable, with mannitol being particularly preferred.

The said lyophilized material can be produced by lyophylizing the alkaline aqueous solution of Compound (I) by use of the method known per se, and in general, lyophilization is preferably carried out by means of a method which comprises freezing the solution at a temperature of below -25° C and drying the freezed material by warming a tray up to 25° C or 40° C at a rate of 5 to 20° C/hr while keeping the degree of vacuum in a dryer at not more than about 0.1 Torr.

The lyophilized material obtained in this manner produces the appearance of white lump form or powder form, and hardly varies in appearance with a length of time elapsed, thereby offering the advantageous characteristic that Compound (I) can be preserved stable for a prolonged period of time.

The said lyophilized material contains a strongly basic substance formulated, and when dissolved in the above-mentioned solvent, produces a solution with a strong alkalinity. In order to adjust the pH of the solution to a physiologically allowable range, consequently, it is preferable to incorporate into the above-mentioned solvent a specifically determined amount of an acidic substance as a pH adjusting agent. Examples of the acidic substance include inorganic acids, such as hydrochloric acid and phosphoric acid, and organic acids, such as succinic acid and tartaric acid, as well as sodium dihydrogenphosphate, glycine, etc. Among others, hydrochloric acid or sodium dihydrogen phosphate is preferable.

Also, it is desirable to formulate an acidic substance in such a way that the pH of the injectable solutions of this invention may be adjusted finally to 7 to 11.

The said solvent having the above-metnioned acidic substance admixed can permit the lyophilized material containing Compound (I) to be dissolved quickly, wherein dissolution or dilution on the occasion of use is preferred.

As the injectable solution of this invention, there may be employed a liquid composition having Compound (I) in conjunction with a strongly basic substance like the previously mentioned ones dissolved in the above-described solvent, which is to be diluted with a solvent being admixed with the above-mentioned acidic substance on the occasion of use to adjust its pH to the physiologically allowable range (ca. 7 to 11).

The thus prepared injectable solution of this invention desirably have the concentration of Compound (I) of 0.1 to 20 mg/ml, particularly 2 to 10 mg/ml.

In addition, it is preferable to incorporate the injectable solution according to the present invention with additives, including buffer solutions for the stablization of its pH, such as arginine, N-methylglucamine, glycine, sodium dihydrogenphosphate, bisodium hydrogen-phosphate, isotonizing agents for the adjustment of its osmotic pressure, such as sodium chloride, stabilizers, such as sodium hydrogensulfite, pain-relieving agents, such as glucose, sorbitol, mannitol, benzyl alcohol, mepivacaine hydrochloride and Xylocaine hydrochloride, and preservatives, such as methyl p-oxybenzoate, propyl p-oxybenzoate, thymelosal and chlorobutanol, as the case may be. These substances can be added usually in an amount of 0.2 to 10 mg, preferably 0.5 to 5 mg, per mg of Compound (I).

In order to enhance the solubility of Compound (I), also there can be formulated sodium chloride, magnesium chloride and potassium chloride. The amount of these salts in the formulation is usually 1 to 30 mg, preferably 3 to 18 mg, per mg of Compound (I).

The injectable solution of this invention is preferably prepared-normally by means of the sterile preparation method known per se.

The injectable solution according to the present invention, preferably, is normally administered intravenously, and its dosage amount is desirably selected in such a way that it may be 5 to 100 mg of Compound (I) daily for male adults, preferably 10 to 50 mg.

In the injectable solution of this invention, the use as a solvent of at least either one out of ethanol, propylene glycol and polyethylene glycol enables Compound (I) slightly soluble in water to solubilize and to be provided with the desired degree of stability. Consequently, it becomes possible to have Compound (I) demonstrate its excellent anti-ulcer activity in an adequate manner.

Below described are the examples to illustrate this invention specifically, but these are not to be understood to limit the scope of this invention.

Example 1

Compound (I-1) was dissolved in ethanol and propylene glycol to the concentration of 2 mg/ml, respectively, and the resulting solutions were sterile filtered and filled in 5-ml portions into ampoules of a 5-ml capacity, followed by sealing.

The test specimens as filled into the ampoules were investigated for appearance, clarity and content of Compound (I) immediately after preparation and after storage at 25°C for 24 hours, with the results being shown in Table 1. The test specimens prepared by dissolution in ethanol and propylene glycol were observed to produce a slight change in appearance after storage at 25°C for 24 hours, but the changes were judged to be so slight that they might in no way influence the injectable solution. The test specimens were found to be stable in terms of content of the active ingredient.

[Table 1] Stability of Compound (I-1) in the solution state:

Composition of test specimen (in 1 ml)	Item of investigation	After preparation	After storage at 25°C/24hrs.
Compound (I-1): 2mg Ethanol : 1ml	Appearance Clarity Content*	Colorless Clear 100.0%	Yellowish Clear 99.2%
Compound (I-1): 2mg Propylene glycol: 1ml	Appearance Clarity Content*	Colorless Clear 100.0%	Light red-purple Clear 103.0%

Note, *: As measured by use of high-performance liquid chromatography (HPLC), whereby the content determined immediately after preparation was taken as 100.0 % (the same method was employed for measurement in examples to be described in the following).

Chromatographic conditions of HPLC:

Carrier;

Nucleosil 5 C_{18} (supplied by Gas-Chro Kogyo K.K. of Japan) 4.0 mm x 150 mm

Solvent;

Methanol:water:triethylamine (60:40:1, pH 7)

Detection method;

UV spectrophotometry at 285 nm

Example 2

Ethanol, polyethylene glycol 400, propylene glycol and water were mixed at the composition ratios as shown in Table 2 illustrated below, and 2 mg of Compound (I-1) was dissolved in 1 ml each of the resulting solvents, respectively, followed by adjustment to pH 9.0 with 5N-aqueous sodium hydroxide solution. As a control, there

were prepared a suspension of 2 mg of Compound (I-1) in 1 ml of water being adjusted to pH 9.0 with 5N-aqueous sodium hydroxide solution and an aqueous solution of 2 mg of Compound (I-1) in 1 ml of 0.01N aqueous sodium hydroxide solution. These solutions were sterile-filtered by the conventional method and were filled in 5-ml portions into ampoules of a 5-ml capacity, respectively, followed by sealing (A control of the suspension was not subjected to sterile-filtration). The test specimens as filled into ampoules were investigated for each item of appearance, pH and content immediately after preparation and after storage at 25°C for 24 hours, with the results being shown in Table 2.

As may be evident from Table 2, all of the test specimens, except the controls, were observed to produce a slight change in appearance after storage at 25° C for 24 hours, but the changes were judged to be so slight that they might in no way influence the injectable solution. In addition, the test specimens were found to show slight change in content. The control specimens, when adjusted to the same pH value as other test specimens, failed to allow adequate dissolution of Compound (I-1), and were needed to be adjusted to a pH of not less than 11 in order to secure dissolution.

[Table 2]

Stability of Compound (I:1) in the solution state

Composition of test specimen (in 1 ml)	Item investigation	After preparation	After storage at 25°C/24 hrs.
Compound (I-1) :2mg	Appearance	Colorless	Slightly to light green-yellow
PEG-400* :0.05ml			
Ethanol :0.35ml	pH	9.0	-
Water :0.6ml	Content	100.0%	98.0%
Compound (I-1) :2mg	Appearance	Colorless	Slightly to light greentoyellow
PEG-400 :0.05ml			
Propylene glycol:0.35ml	pH	9.0	-
Water :0.6ml	Content	100.0%	94.4%
Compound (I-1) :2mg	Appearance	Colorless	Slightly to light green-yellow
PEG-400 :0.4ml	pH	9.0	-
Water :0.6ml	Content	100.0%	91.8%
Compound (I-1) :2mg	Appearance	Colorless	Slightly to light red-purple
Ethanol :0.5ml	pH	9.0	-
Propylene glycol:0.5ml	Content	100.0%	98.0%
Compound (I-1) :2mg	Appearance	White suspension	Slightly to light grey suspension
Water :1ml	pH	9.1	-
	Content	-	-
Compound (I-1):2mg	Appearance	Colorless	Colorless
0.01N aq. sodium	pH	11.4	-
hydroxide sol'n.:1ml	Content	100.0%	92.5%

Note, *; Polyethylene glycol having an average molecular weight of 400.

Example 3

Ethanol, polyethylene glycol 400, propylene glycol and water were mixed at the composition ratios as shown in Table 3 illustrated below, and 5mg of Compound (I-1) was dissolved in 1 ml each of the resulting solvents, respectively, followed by adjustment to pH 9.0 with 5N-aqueous sodium hydroxide solution. As a control, there were prepared a suspension of 5 mg of Compound (1-1) in 1 ml of water being adjusted to pH 90 with 5N-aqueous sodium hydroxide solution and an aqueous solution of 5 mg of Compound (I-1) in 1 ml of 0.02N aqueous sodium hydroxide solution. These solutions were sterile-filtered by the conventional method and were filled in 5-ml portions into ampoules of a 5-ml capacity, respectively, followed by sealing (A control of the suspension was not subjected to sterile-filtration).

These test specimens as filled into ampoules were investigated for each item of appearance, pH and clarity

Immediately after preparation and after storage at 25°C for 24 hours, with the results being shown in Table 3.

As may be evident from Table 3, all of the test specimens, except the controls, were observed to produce a slight change in appearance after storage at 25°C for 24 hours, but the changes were judged to be so slight that they might in no way influence the injectable solution. In addition, they were observed to shown no change in clarity. The control specimens, when adjusted to the same pH value as other test specimens, failed to allow adequate dissolution of Compound (I-1) and were needed to be adjusted to a pH of not less than 11 in order to secure dissolution.

[Table 3]

Stability of Compound (I-1) in the solution state

Composition of test specimen (in 1ml)	Item of investigation	After preparation	After storage at 25°C/24 hrs.
Compound (I-1) :5mg	Appearance	Colorless	Slightly to light green-yellow
Ethanol :0.6ml	pH	9.0	-
Water :	Clarity	Clear	Clear
Compound (I-1):5mg	Appearance	Colorless	Slightly to light green-yellow
PEG-400* :0.4ml	pH	9.0	-
Water :0.6ml	Clarity	Clear	Clear
Compound (I-1) :5mg	Appearance	Colorless	Slightly to light green-yellow
Ethanol :0.3ml	pH	9.0	-
Propylene glycol:0.3ml	Clarity	Clear	Clear
Water :0.4ml			
Compound (I01) :5mg	Appearance	Colorless	Slightly to light green-yellow
PEG-400 :0.3ml	pH	9.0	-
Ethanol :0.3ml	Clarity	Clear	Clear
Water :0.4ml			
Compound (I-1) :5mg	Appearance	White suspension	Slightly to light grey suspension
	pH	8.9	-
Water :1ml	Clarity	-	-
Compound (I-1):5mg	Appearance	Colorless	Colorless
0.02N-aq. sodium	pH	11.6	
hydroxide sol'n.:1ml	Clarity	Clear	Clear

Note, *; Polyethylene glycol having an average molecular weight of 400.

Example 4

A 1000 mg quantity of Compound (I-1) was dispersed in distilled water for injection, and 3 ml of 1N-aqueous sodium hydroxide solution was added to dissolve the Compound (I-1), followed by addition of water to make up to the total of 50 ml and sterile filtration by the conventional method. The resulting filtrate was filled in 1 ml portions into vials of a 12 cm^3 capacity, followed by lyophilization by means of the conventional technique. The lyophilized powder as contained in vials was dissolved in in Solvent A (which was composed of 50 mg of N-methylglucamine, 0.27 ml of 1N-hydrochloric acid and 2 ml of propylene glycol being admixed with ethanol to make up to the total of 4 ml), Solvent B (which was composed of 50 mg of N-methylglucamine, 0.27 ml of 1N-hydrochloric acid, 1.2 ml of polyethylene glycol 400 and 1.2 ml of ethanol being admixedwith distilled water for injection to make up to the total of 4 ml), Solvent C (which was composed of 50 mg of N-methylglucamine, 0.27 ml of 1N-hydrochloric acid, 1.2 ml of ethanol and 1.2 ml of propylene glycol being admixed with distilled water for injection to make up to the total of 4 ml) and Solvent D (which was composed of 50 mg of N-methylglucamine, 0.27 ml of 1N-hydrochloric acid and 2.5 ml of polyethylene glycol 400 bing admixed with distilled water for injection to make up to the total of 4 ml), respectively, to perform inspection for their solubilities as well as to conduct investigation into appearance clarity and contents immediately after dissolution and after storage at 25°C for 24 hours.

The results are shown in Table 4. The lyophilized powder showed excellent solubilities in all of these Solvents, and were able to be dissolved quickly. In addition to this, the resulting solutions were observed to produce slight changes in appearance immediately after dissolution and after storage for 24 hours, but the changes were found to be so slight that they might in no way influence the injectable solution. The solutions were found to show no change in the clarity while being observed to decrease slightly in content of Compound (I-1).

[Table 4] Stability of the lyophilized Compound (I-1) after being dissolved in vials:

Item \ Solvent	A	B	C	D
Solubility	Good	Good	Good	Good
pH after dissolution	8.7	9.0	9.0	9.0
After dissolution:				
Appearance	Colorless	Colorless	Colorless	Colorless
Clarity	Clear	Clear	Clear	Clear
Content	100%	100%	100%	100%
After storage at 25°C for 24 hrs.:				
Appearance	Slightly to lightly green-yellow			
Clarity	Clear	Clear	Clear	Clear
Content	97.0%	96.5%	96.7%	16.1%

Example 5

There were prepared 100 ml each of three kinds of aqueous solutions containing Compound (I-1), mannite and sodium hydroxide at the individually different compositions per ml as shown in Table 5. The resulting aqueous solutions were sterile-filtered by the conventional method, and the filtrates were filled in 2 ml portions into vials of a 18 cm^3 capacity, respectively, followed by lyophilization by the conventional technique to give three kinds of lyophilized vials (V1, V2 and V3) having the formulations as shown in Table 6.

Then, there were prepared 500 ml each of five kinds of aqueous solutions containing PEG-400, sodium chloride, N-methylglucamine, sodium bihydrogenphosphate, hydrochloric acid and sodium hydroxide at the individually different compositions per each 10 ml as shown in Table 7. The aqueous solutions were sterile-filtered by the conventional method, and the resulting filtrates were filled in 10 ml portions into ampoules of a 10 ml capacity, respectively. The ampoules were sealed and sterilized by high-pressure steam at 115°C for 30 minutes to give five kinds of the solutions for dissolution (S1, S2, S3, S4 and S5) having the individual formulations as shown in Table 7.

Following the combinations as described in Table 8, then, the lyophilized vials were dissolved again in the solutions for dissolution, and the resulting drug solutions were investigated for pH and clarity immediately after preparation and after storage at 25°C for 24 hours. As may be evident from the results shown in Table 8, the drug solutions resulting from any of the combinations were found to be stable in pH and good in clarity, whereby the lyophilized vials after being dissolved by any of the combinations exhibited good solubility.

[Table 5] Composition of the aqueous solution to be filled into vials (in 1 ml)

Ingredient \ No.	1	2	3
Compound (I-1)	15 mg	15 mg	15 mg
Mannitol	15 mg	15 mg	15 mg
Sodium hydroxide	2.4 mg	2.4 mg	4.8 mg
Distilled water for injection	Suitable volume to make up to the total of 1 ml.		

[Table 6] Composition of the lyophilized vials (per vila)

Ingredient \ No.	V1	V2	V3
Compound (I-1)	30 mg	30 mg	30 mg
Mannitol	30 mg	100 mg	30 mg
Sodium hydroxide	4.8 mg	4.8 mg	9.6 mg

[Table 7] Compositions after being dissolved (per 10 ml)

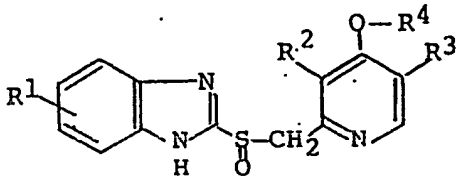
Ingredient \ No.	S1	S2	S3	S4	S5
PEG-400	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
Sodium chloride	90 mg	90 mg	90 mg	90 mg	90 mg
N-methylglucamine	10 mg	40 mg	40 mg	-	-
$NaH_2PO_4 \cdot 2H_2O$	-	-	-	13 mg	50 mg
Hydrochloric acid	1.1 mg	7.7 mg	8.4 mg	-	-
Sodium hydroxide	-	-	-	2.8 mg	11 mg
pH	9.0	3.1	8.5	8.5	7.0

[Table 8] Stability after dissolution of lyophilized vials containing Compound (I-1)

Combination / Sta-bility	Immediately after preparation		After storage at 25°C for 24 hrs.	
Vial	Solution for diss'n	pH	Clarity	pH	Clarity
V1	S1	9.8	Clear	9.8	Clear
V2	S1	9.9	Clear	9.8	Clear
V3	S2	10.1	Clear	9.9	Clear
V1	S4	9.9	Clear	10.0	Clear
V2	S4	10.2	Clear	10.0	Clear
V3	S5	10.0	Clear	9.9	Clear

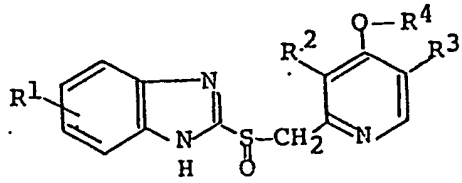
Claims

1. An injectable solution characterized by containing (a) a compound of the formula;



wherein R^1 represents hydrogen, methoxy or trifluoromethyl group; R2 and R^3, being the same as or different from each other, represent hydrogen or methyl group; and R^4 represents a fluorinated C_2 to C_5 lower alkyl group, and (b) at least one of ethanol, propylene glycol and polyethylene glycol.

2. An injectable solution which comprises a solution wherein a freeze-dried material of an alkaline aqueous solution of a compound represented by the formula;



wherein R^1 represents hydrogen, methoy or trifluoromethyl group; R^2 and R^3 , being the same as or different from each other, represent hydrogen or methyl group; and R^4 represents a fluorinated C_2 to C_5 lower alkyl group, has been dissolved with a mixed solution of (a) an acidic substance and (b) at least one of ethanol, propylene glycol and polyethylene glycol.

3. An injectable solution as claimed in claim 2, wherein the freeze-dried material is a freeze-dried material of the alkaline aqueous solution containing a saccharide besides the compound.

4. An injectable solution as claimed in claim 3 wherein the saccharide is mannitol.

5. An injectable solution as claimed in claim 2 or 3, wherein the acidic substance is hydrochloric acid or sodium dihydrogenphosphate.

6. An injectable solution as claimed in claim 2, wherein the polyethylene glycol is polyethylene glycol 400.

7. An injectable solution as claimed in claim 2, wherein the mixed solution additionally contains N-methylglucamine.

8. An injectable solution as claimed in claim 2, wherein the mixed solution additionally contains sodium chloride.

9. An injectable solution as claimed in claim 2, wherein the mixed solution additionally contains N-methylglucamine and sodium chloride.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 8352

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	J. PHARM. PHARMACOL., vol. 36, 1984, pages 470-472, J. Pharm. Pharmacol.; L.K. WEBSTER et al.: "Effect of omeprazole and polyethylene glycol-400 on antipyrine elimination by the isolated perfused rat liver" * Page 470, abstract * ---	1-6,8	A 61 K 31/44 A 61 K 47/00 A 61 K 9/00
Y	EP-A-0 237 200 (TAKEDA CHEMICAL INDUSTRIES LTD) * Claims * ---	1-9	
Y	DE-A-1 804 450 (EGYESÜLT GYOGYSZER-ES TAPSZERGYAR) * Pages 1,2; claims * -----	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06-11-1989	BERTE M.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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